Changes in calf muscle deoxygenation after foam sclerotherapy in patients with superficial venous insufficiency

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Objective: **This study assessed changes in the calf muscle deoxygenated hemoglobin (HHb) level during light-intensity exercise after ultrasound-guided foam sclerotherapy (UGFS) for superficial venous insufficiency.**

Methods: **UGFS with 1% or 3% polidocanol foam (POL-F) was used to treat unilateral great saphenous vein reflux in 84 patients. Near-infrared spectroscopy (NIRS) was used to measure calf muscle HHb levels before and 3 months after UGFS. The calf venous HHb blood-filling index was calculated on standing, the calf venous HHb ejection index was obtained after one tiptoe movement, and the venous HHb retention index was obtained after 10 tiptoe movements. The primary end point was an evident improvement in calf muscle deoxygenation after UGFS. The secondary end point was obliteration of the great saphenous vein.**

Results: **Treatment consisted of 1% POL-F in 48 limbs and 3% POL-F in the remaining 36. Ultrasound imaging at the 3-month follow-up demonstrated complete occlusion in 56.3% of the patients who received injections of 1% POL-F and in 66.7% of those who received injections of 3% POL-F. The difference in treatment outcome between the groups was not significant ($P = .333$). Reflux was absent in 39 limbs (81.3%) treated with 1% POL-F and in 34 limbs (94.4%) treated with 3% POL-F, and no significant difference was observed between the two groups ($P = .076$). Postsclerotherapy NIRS demonstrated significant reductions in the levels of the HHb filling index in both treatment groups ($P = .039$, $P = .0001$, respectively) and significant reductions in the levels of the HHb retention index ($P < .0001$, $P = .008$, respectively). However, the differences in the levels of the HHb ejection index before and after UGFS were not significant ($P = .250$, $P = .084$, respectively).**

Conclusions: **Our present findings suggest that changes in the values of these parameters may be of potential use for assessing the effects of foam sclerotherapy in patients with superficial venous insufficiency. (J Vasc Surg 2012;56:1649-55.)**

Recent advances in the field of phlebology have led to a decrease in the use of invasive techniques for the diagnosis of chronic venous insufficiency (CVI). Duplex ultrasound scanning augmented by color-flow Doppler imaging has been developed over the last 2 decades and has almost replaced invasive venography. An ultrasound-derived reflux time (RT) of >0.5 seconds has been used as the gold standard for evaluation of venous reflux.[1-3] However, recent studies have shown that peak reflux velocity (PRV) better correlates with the clinical severity of CVI than individual or total RT.[4-9]

Near-infrared spectroscopy (NIRS) is a noninvasive optical method that was developed for determining tissue oxygenation and hemodynamics. Using a modification of the Lambert-Beer law,[10] it is now possible to obtain quantitative values for the levels of total hemoglobin (Hb), oxygenated hemoglobin (O_2Hb), and deoxygenated hemoglobin (HHb). NIRS measurements primarily reflect changes in the small arterioles, capillaries, and venules.[11] Several investigators have demonstrated a correlation between the severity of CVI and changes in HHb and showed that NIRS might be useful for assessment of ambulatory venous function in patients with CVI.[12-14]

Huge advances have also been made in the management of venous diseases. Invasive stripping operations have gradually been replaced by endogenous thermal and chemical ablations that can reduce operative morbidity and recovery time. Although ultrasound-guided foam sclerotherapy (UGFS) has been recognized as a common treatment option for patients with superficial CVI, no studies have attempted to define the relationship between the changes in HHb and clinical improvement after UGFS. The purpose of the present study was to define how foam sclerotherapy for superficial CVI affects the values of parameters determined by NIRS in the lower extremities.

METHODS

The UGFS treatment used in this study was approved by the Institutional Review Board, and informed consent was obtained from all participants.

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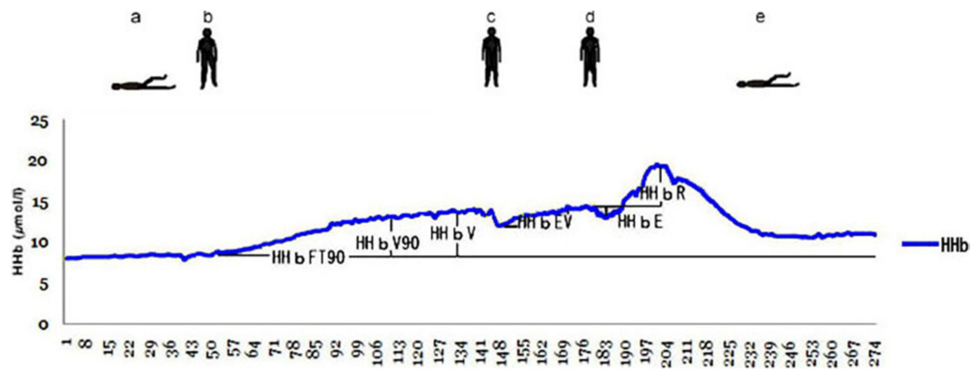

Fig 1. The near-infrared spectroscopy examination assesses various deoxygenated hemoglobin (*HHb*) variables. Calf venous blood-filling index (*FI-HHb*) was calculated by dividing 90% of the venous blood volume (*HHbV90*) by the time taken to fill 90% of the venous volume (*HHbFT90*). After (**a**) resting, the patient was asked to (**b**) stand and perform **(c)** one tiptoe movement with weight-bearing on both legs, which produced an ejected volume (*HHbEV*), and then to return to the initial position, the changes in HHb being observed. The calf venous ejection index (*EI-HHb*) was calculated as HHbEI = HHbEV/HHbV. After a new plateau had been reached, the patient performed **(d)** 10 tiptoe movements, allowing venous expulsion (*HHbE*) and subsequent retention (*HHbR*), and then returned to the **(e)** resting position. The venous retention index (*RI-HHb*) was determined as HHbRI = HHbR/HHbE.

Patients. The study comprised 84 patients (24 men; 60 women), with a mean age of 65.4 years (range, 45-82 years), who were treated for great saphenous vein (GSV) reflux associated with saphenofemoral junction (SFJ) incompetence between March 2010 and June 2010. Among the 84 patients, 48 received UGFS using 1% polidocanol foam (POL-F), and the remaining 36 received UGFS using 3% POL-F. Patients' height, weight, and body mass index (kg/m^2) were recorded, as well as CEAP scores.[15] All patients examined in this study were classified as $C_{2,3,4a}$, E_p, A_s, $P_{r2,3}$. The study excluded patients with myocardial ischemia, arterial insufficiency, those with an ankle-brachial index of <0.9, in the first trimester of pregnancy and after the 36th week of gestation, local infection in the area scheduled for sclerotherapy, active thrombophlebitis, and acute deep vein thrombosis.

Pretreatment evaluation. Pretreatment venous reflux examination was performed using a color duplex scanner (LOGIQ 7 PRO; GE Healthcare, Japan, Tokyo, Japan) at the SFJ and in the GSV using a 5- to 10-MHz transducer. Venous reflux was assessed while the patient was standing. For evaluation of the SFJ, a pneumatic thigh cuff (Hokanson, Bellevue, Wash) was attached to the thigh, inflated to 80 mm Hg, and then rapidly deflated. For evaluation of the GSV, the transducer was placed 10 cm above knee level, and a cuff was applied to the calf, inflated to 100 mm Hg, and then rapidly deflated. The diameter of the GSV was measured in cross-sectional view 3 to 4 cm distal to the SFJ with the patient standing. Venous reflux was considered to be present if the RT >0.5 seconds.

The details of the NIRS examination protocol have been described previously.[14,16-18] The light source of the device (OM-200; Shimadzu Co, Kyoto, Japan) consists of three laser beams with different wavelengths (780, 805, and 830 nm). According to the variations in optical density at each wavelength, O_2Hb, HHb, and total Hb are calculated on the basis of the Lambert-Beer law,[10] allowing changes in the concentration of Hb to be calculated. Our instrument had a probe containing the light source and two separate detectors fixed at 25 mm and 40 mm from the source. A review by McCully and Hamaoka[19] has shown that light travels in a shallow arc to a penetration depth of about one-half the separation distance into the tissue. The light emitter-detector distance of the probe used in our study was 40 mm, so the penetration depth was estimated to be 20 mm. Changes in the hemoglobin concentration were expressed as absolute values in micromols per liter.

For assessment of ambulatory venous function, measurements were carried out using the same standard exercise protocol as that for air plethysmography (Fig 1). The sensor was placed firmly on the posterior aspect of the calf, over the medial head of the gastrocnemius muscle, using adhesive tape. The patient rested supine initially for 5 minutes with the leg elevated on a foam block. The patient then stood without putting any weight on the leg being studied, resulting in an increase of HHb concentration as the veins filled. The patient was then asked to keep still until an HHb volume (HHbV) plateau had been reached. The calf venous blood-filling index (FI-HHb; μmol/L/s) was calculated by dividing 90% of the venous blood volume (HHbV) by the time taken to fill 90% of the venous volume. Then, the patient was asked to perform one tiptoe movement with weight-bearing on both legs, which produced an ejected volume (HHbEV), and then return to the initial position, the change in HHb being observed. The calf venous ejection index (EI-HHb) was calculated as HHbEI = HHbEV/HHbV.

After a new plateau had been reached, the patient was asked to perform 10 tiptoe movements to achieve venous expulsion (HHbE) and a subsequent retention (HHbR).

The venous retention index (RI-HHb) was determined as HHbRI = HHbR/HHbE. Our previous study had shown that the combination of FI >0.2 and RI >2.9 improved the ability to discriminate early from advanced CVI, wth a sensitivity of 94% and a specificity of 86%.[17]

UGFS procedure. The sclerosant foam was prepared by Tessari's method using 1% or 3% POL (Polidocasclerol; Zeria Pharmaceutical Co Ltd, Tokyo, Japan). Details of the methods used for foam sclerotherapy were described previously.[20] The patients were placed supine with their affected leg elevated 30°, and each visible varicose tributary vein was injected first using 23-gauge butterfly needles. All patients received <0.5 mL POL foam per injection to minimize any foam migration beyond the target vein.[20] Subsequently 1% or 3% POL-F was injected into the GSV under ultrasound guidance using a 21-gauge venous catheter. The GSV cannulae were inserted before injection of the tributaries. The total amount of injected foam did not exceed 10 mL in any of the cases.[21]

After completion of foam sclerotherapy, compression pads and elastic bandages were applied and kept on continuously for the first 2 days. All patients were encouraged to ambulate after the treatment. On day 3 after UGFS, the elastic bandages and compression pads were removed, and a class II thigh-high compression stocking was applied.

Follow-up after UGFS. To investigate the changes in the values of calf muscle HHb, postsclerotherapy surveillance was done at 3 months using NIRS. Duplex scanning was done at 3 months to evaluate the efficacy of UGFS. The results of duplex ultrasound imaging were classified as follows:

1. Complete occlusion: the GSV had shrunk and was occluded.
2. Partial GSV recanalization with no reflux.
3. Partial GSV recanalization with reflux.
4. Complete GSV recanalization with reflux.

The primary end point of this study was an evident improvement in calf muscle deoxygenation after UGFS. The secondary end point was obliteration of the GSV.

Statistical analysis. All data were analyzed using SPSS 16.0 software (SPSS Inc, Chicago, Ill). Comparisons of numerical data between groups of patients were made using Student *t*-test, and χ^2 contingency table analysis was used to evaluate differences between proportions. Continuous data are expressed as mean ± standard deviation. Statistical significance was defined as $P < .05$.

RESULTS

Patient characteristics. Table I summarizes the baseline characteristics of the two study groups, which did not differ significantly in age (P = .587), the male-to-female ratio (P = .889), or in height (P = .945), weight (P = .555), or body mass index (P = .430). The mean GSV diameter was 6.5 ± 1.5 mm for the 1% POL-F group and 6.9 ± 1.6 mm for the 3% POL-F group, which was not significantly different (P = .181). There was also no significant intergroup difference in each CEAP class (C_2, P = .630; C_3, P = .836; C_{4a}, P = .554), with 79.2% of 1% POLF-F patients and 83.3% of 3% POL-F patients at C_2 (uncomplicated varicose veins). Successful cannula placement and ultrasound-monitored foam injection were accomplished in all patients without any immediate complications.

Table I. Baseline characteristics of the patients receiving 1% or 3% polidocanol foam (*POL-F*)

Variables[a]	*1% POL-F (n = 48)*	*3% POL-F (n= 36)*	P
Age, year	64.7 ± 8.9	66.3 ± 8.8	.587
Female sex	34 (70.8)	26 (72.2)	.889
Height, m	1.60 ± 0.07	1.60 ± 0.08	.945
Weight, kg	56.7 ± 10.6	59.2 ± 9.4	.555
Body mass index, kg/m^2	22.1 ± 3.5	23.0 ± 2.7	.430
GSV diameter, mm	6.5 ± 1.5	6.9 ± 1.6	.181
CEAP C classification[b]			
C_2	38 (79.2)	30 (83.3)	.630
C_3	1 (2.1)	1 (2.8)	.836
C_{4a}	9 (18.7)	5 (13.9)	.554

GSV, Great saphenous vein.
[a]Continuous data are shown as mean ± standard deviation, and categoric data as number (%).
[b]CEAP C classification: C_2, varicose veins; C_3, edema without skin changes; C_{4a}, pigmentation or eczema.

Changes in NIRS-derived parameters before and after UGFS. NIRS after UGFS demonstrated significant reductions in the levels of FI-HHb in both treated groups (P = .039 and P = .0001, respectively; Figs 2, *A* and 3, *A*) and significant reductions in the levels of RI-HHb ($P <$ .0001, P = .008, respectively; Figs 2, *C* and 3, *C*). However, there was no significant difference in the levels of EI-HHb before and after UGFS (P = .250 and P = .084, respectively; Figs 2, *B* and 3, *B*).

Outcome of UGFS. Table II reports the findings obtained by duplex ultrasound imaging 3 months after the treatment. Complete occlusion was demonstrated in 56.3% of the patients who received injections of 1% POL-F and in 66.7% of those who received injections of 3% POL-F, there being no significant difference in treatment outcome between the groups (P = .333). Similarly, 25.0% of the patients who received 1% POL-F and 27.7% of those who received 3% POL-F showed partial recanalization with no reflux (P = .775). Patients who received 3% POL-F had a higher success rate, but this was not statistically significant (P = .076). In contrast, 18.7% of the patients who received 1% POL-F showed reflux in the GSV 3 months after treatment. Similarly, 5.6% of the patients in the 3% POL-F group showed reflux in the treated GSV.

DISCUSSION

This study investigated the effect of UGFS on calf muscle deoxygenation in patients with superficial CVI. We found that 1% POL-F and 3% POL-F were as equally effective for the treatment of GSV reflux, with 79% of the 1% POL-F group and 83% of the 3% POL-F group having uncomplicated varicose veins (CEAP C_2), and that there

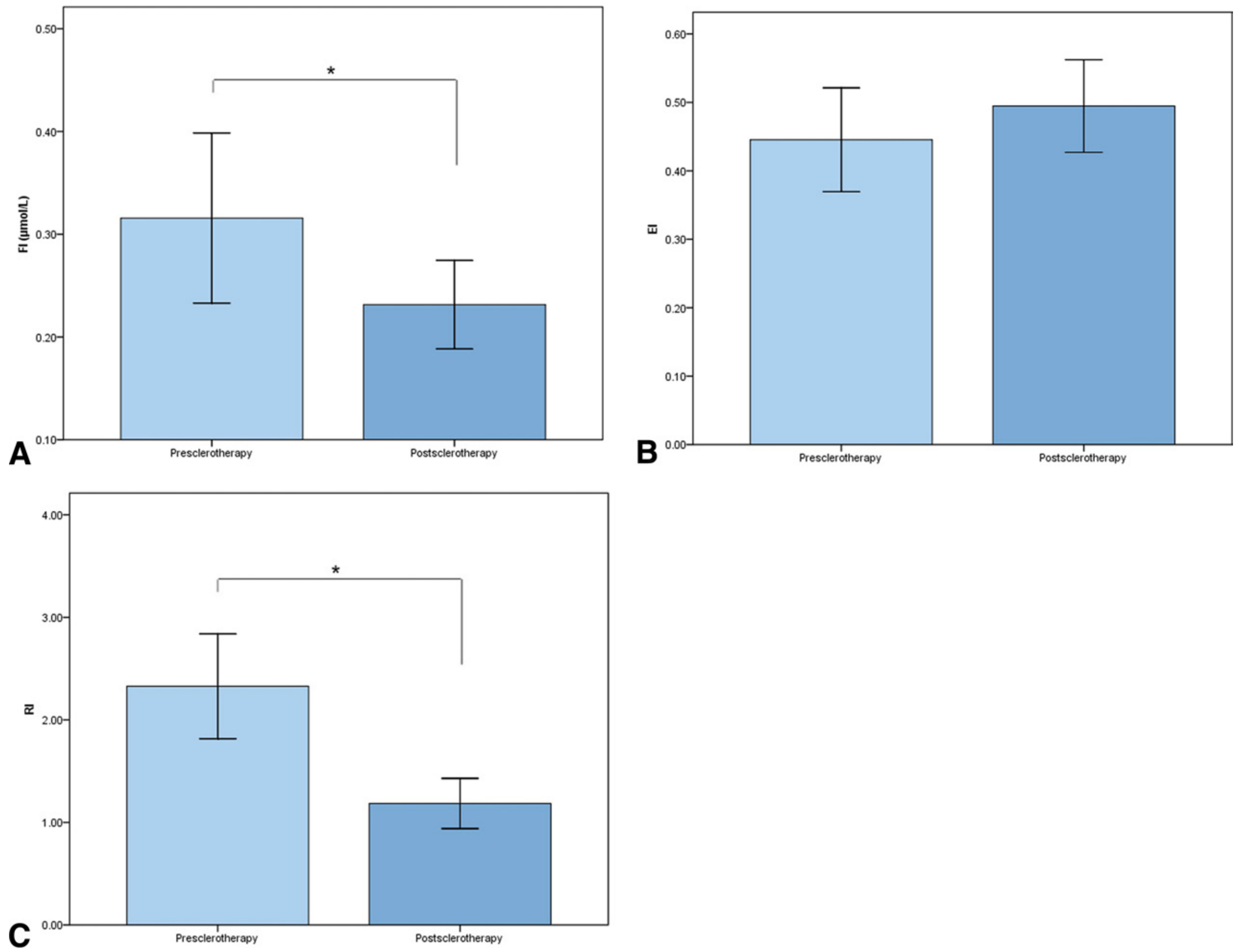

Fig 2. Changes in the near-infrared spectroscopy-derived deoxygenated hemoglobin (HHb) parameters are shown before and after 1% polidocanol foam (POL-F) sclerotherapy. **A,** Near-infrared spectroscopy demonstrated significant reduction in the level of the calf venous blood-filling index (*FI*; $P = .039$). **B,** There was no significant difference in the level of the calf venous ejection index (*EI*) before and after foam sclerotherapy ($P = .250$). **C,** There was a significant reduction in the level of the venous retention index (*RI*) after foam sclerotherapy ($P < .0001$).

were significant reductions in the values of FI-HHb and RI-HHb after UGFS but no significant changes in the value of EI-HHb.

The safety and efficacy of UGFS as a minimally invasive treatment for varicose veins has become widely accepted, and a number of large case series have been reported.[22-26] The use of an appropriate concentration and volume of foam sclerosant yields good short-term GSV occlusion rates. At the Second European Consensus Meeting on Foam Sclerotherapy (ECMFS), most experts reported using 3% POL to prepare foam for the treatment of GSV reflux.[21]

However, recent studies comparing 1% and 3% POL-F found that the two concentrations were equally effective when the GSV trunk diameter was <8 mm.[27,28] Hamel-Desnos et al[27] reported that after 3 weeks, reflux was abolished in 96% of patients who received 3% POL-F and in 88% of those who received 1% POL-F, with no significant intergroup difference in the success rate. Even after 2 years, reflux was absent in 69% of the 3% group and in 68% of the 1% group, the success rate again showing no significant intergroup difference.[27]

Similarly, Blaise et al[28] found that at 6 months, venous reflux was abolished in 69% of patients who received 1% POL-F and in 85% of those who received 3% POL-F; the corresponding figures at 3 years were 79% and 78%, respectively. The authors thus concluded that 1% and 3% POL-F had equivalent efficacy for treatment of GSV incompetence.[28]

Nevertheless, Ceulen et al[29] suggested that there was a clinically relevant, but nonsignificant, difference between 1% and 3% POL-F in the proportion of patients achieving GSV occlusion (69.5% vs 80.1%). After 1 year of follow-up, they concluded that the use of 3% POL-F was more effective in terms of absence of reflux and disappearance of complaints. In the present study, we found no significant difference of effectiveness between 1% and 3% POL-F,

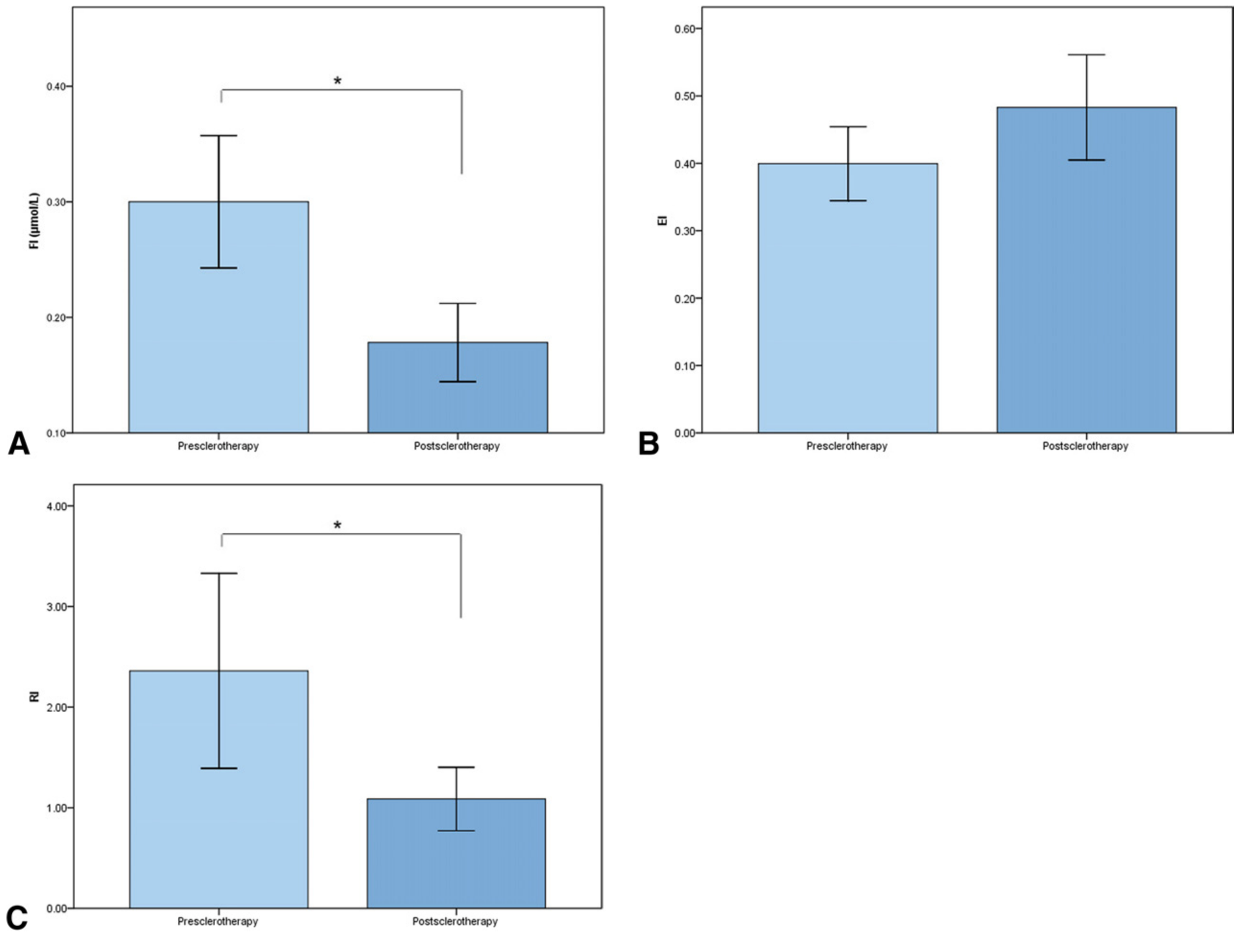

Fig 3. Near-infrared spectroscopy-derived parameters of deoxygenated hemoglobin (HHb) are shown before and after 3% polidocanol foam (POL-F) sclerotherapy. **A,** Near-infrared spectroscopy demonstrated significant reduction in the level of calf venous blood-filling index (*FI*; $P = .0001$). **B,** There was no significant difference in the level of the calf venous ejection index (*EI*) before and after foam sclerotherapy ($P = .084$). **C,** There was a significant reduction in the level of venous retention index (*RI*) after sclerotherapy ($P = .008$).

Table II. Outcome of ultrasound-guided foam sclerotherapy with 1% or 3% polidocanol foam (*POL-F*)

Outcome	*1% POL-F (n = 48) No. (%)*	*3% POL-F (n = 36) No. (%)*	P
Occlusion	27 (56.3)	24 (66.7)	.333
Partial recanalization with no reflux	12 (25.0)	10 (27.7)	.775
Subtotal	39 (81.3)	34 (94.4)	.076
Partial recanalization with reflux	9 (18.7)	2 (5.6)	.076
Complete recanalization with reflux	0	0	. . .
Subtotal	9 (18.7)	2 (5.6)	.076
Total	48 (100)	36 (100)	

although 3% POL-F appeared to better facilitate occlusion and elimination of reflux. This suggests that 3% POL-F may be a better sclerosant, even though POL-F at both 1% and 3% is effective for treatment of superficial venous insufficiency.

Although most studies have set the primary end point of UGFS as obliteration or elimination of reflux, few have investigated the functional outcome after foam sclerotherapy. Yamaki et al[23] used air plethysmography to compare functional outcome between UGFS and ultrasound-guided liquid sclerotherapy. They found that venous filling index values remained normal during subsequent follow-up after UGFS, whereas the venous filling index began to increase after ultrasound-guided liquid sclerotherapy and the difference was significant at 6 months ($P < .0005$). At 9 months, they also found that there was a significant difference in the residual volume fraction between the two groups and that the residual volume fraction continued to improve after UGFS ($P = .033$).

Brunken et al[30] used photoplethysmography and strain-gauge plethysmography to investigate changes in venous function after UGFS. They found a significant increase in venous refilling time ($P = .00003$) and a decrease in venous capacity ($P = .0007$) after UGFS.[30] Similarly, Darvall et al[31] used digital photoplethysmography to show that the median venous refilling time improved significantly after UGFS ($P < .0005$).[31]

Since the first observations of tissue oxygenation using NIRS by Jöbsis,[32] this technique has been subsequently refined and applied to the study of cerebral hemodynamics.[33-38] By choosing an accurate distance between source and detector, NIRS can provide direct measurements for any muscle of interest. During the last 2 decades, numerous studies have developed and refined the NIRS approach for studying skeletal muscular hemodynamics and metabolism in vivo.[39-43] Attempts have also been made to apply NIRS to venous hemodynamics in patients with CVI. Hosoi et al[12] first applied this modality for assessment of hemodynamics in patients with CVI. They used the ambulatory venous RI obtained from the serial changes in HHb and found that NIRS was useful for evaluation of ambulatory venous dysfunction.[12] Later, they studied patients with symptomatic post-thrombotic syndrome and found that the degree of ambulatory venous RI was correlated well with clinical severity.[13]

We have previously investigated the correlation of clinical severity and ultrasound-guided reflux parameters with NIRS-derived parameters in patients with CVI. We found that (1) FI and RI measured by NIRS were increased in patients with advanced CVI, (2) EI measured by NIRS was significantly reduced in patients with deep CVI alone compared with superficial CVI alone, (3) ultrasound-derived PRV showed a better positive correlation with NIRS-derived RI in the SFJ, GSV, and popliteal vein and with EI in the gastrocnemius vein, and (4) a combination of FI >0.2 and RI >2.9 significantly improved the ability to discriminate early from advanced CVI.[17]

It was of interest that we found a poor correlation between NIRS-derived parameters and ultrasound-derived RT. NIRS-derived RI appeared to better reflect the severity of venous reflux and was vastly superior to ultrasound-guided RT. This was further supported by the observation that NIRS-derived RI was significantly correlated with ultrasound-derived PRV, which is regarded as a useful parameter for discrimination of clinical severity. Among the parameters evaluated in the present study, NIRS-derived FI and RI appeared promising for assessing the effects of UGFS in patients with superficial CVI. Furthermore, we found that increased RI was predictive of the development of post-thrombotic syndrome in patients with a first episode of deep vein thrombosis.[16,17] Follow-up for a much longer period may reveal whether increased calf muscle deoxygenation after UGFS is predictive of varicose vein recurrence.

Our study had some potential limitations. In particular, the 3-month follow-up period was too short to allow a full evaluation of the efficacy of UGFS. In addition, the limited sample size could have introduced a type II statistical error. Finally, repetitive examinations may be required to confirm the usefulness of NIRS for follow-up of patients receiving UGFS.

CONCLUSIONS

NIRS after foam sclerotherapy demonstrated significant reductions in the levels of FI and RI in patients treated with 1% POL-F or 3% POL-F. Measurement of these parameters by NIRS was simple and noninvasive, and was able to indicate functional improvement after foam sclerotherapy in patients with superficial venous insufficiency.

AUTHOR CONTRIBUTIONS

Conception and design: TY
Analysis and interpretation: TY
Data collection: HK, DF, KO, AO, AH
Writing the article: TY
Critical revision of the article: TY, MN, HS
Final approval of the article: TY, HK, DF, KO, AO, AH, MN, HS
Statistical analysis: TY
Acquisition of funding: Not applicable
Overall responsibility: TY

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